Morse (J. L.)

REMARKS ON THE CLASSIFICATION

OF THE

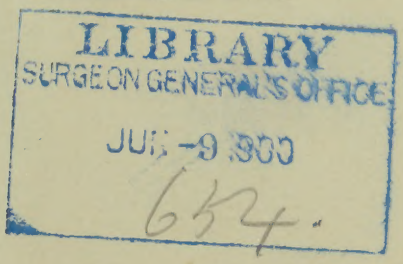
ANÆMIAS OF INFANCY,

WITH A REPORT OF A SEVERE CASE.

BY

JOHN LOVETT MORSE, A.M., M.D.,

Physician to Out-Patients at the City Hospital and at the Infants' Hospital, Boston. Assistant in Clinical Medicine, Harvard Medical School.



REMARKS ON THE CLASSIFICATION OF THE ANÆMIAS OF INFANCY, WITH A REPORT OF A SEVERE CASE.*

BY JOHN LOVETT MORSE, A.M., M.D.,

Physician to Out-Patients at the City Hospital and at the Infants' Hospital, Boston. Assistant in Clinical Medicine, Harvard Medical School.

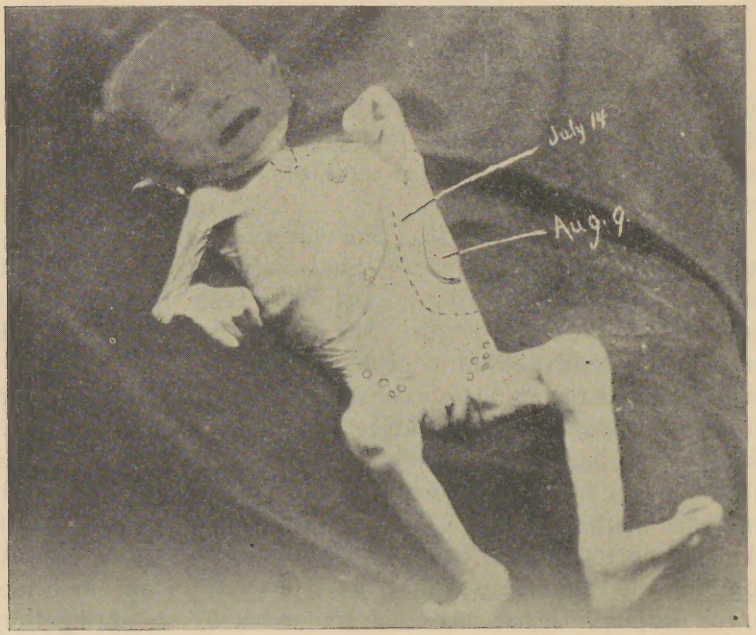
Alice C., ten months old, was brought to the Infants' Hospital July 14, 1897. The parents were Canadians and well. Of eleven older children, seven had died of various troubles; the remainder were well. There was no tubercular or syphilitic history.

She was healthy at birth. She was never nursed, but was fed on various "infant foods." She never thrived, and gained little or no weight. During the last few weeks she had rapidly lost both weight and strength. She had always vomited a good deal, less recently. Had considerable diarrhœa for first few months; since then moderate constipation, the movements being normal in color. Always subject to cough; more so lately. Said to have had pneumonia at eight months. Bunches were noticed in the neck and groins at five months. They had not increased markedly since. Depression of fontanelle, dryness of skin and nocturnal fever had been present for three months. A tumor in the abdomen was first noted a week before she came to the hospital. It had increased somewhat in size during this time. There had been no internal or subcutaneous hemorrhages.

PHYSICAL EXAMINATION.—Poorly developed and emaciated. Skin dry and generally brownish, but pigmentation nowhere localized. No subcutaneous hemorrhages. Frontal bones at a considerably lower level than parietal. Parietal eminences large. Fontanelle depressed, but small. No teeth. Tonsils normal. Whitish bunch, size of a small pea, in median line at junction of hard and soft palate. Slight rosary. Heart and lungs normal. Thyroid not enlarged. Dulness under upper part of sternum. No dulness at root of lungs. Numerous small glands both anterior and posterior to sterno-mastoid muscles. Glands in axillæ, size of pea. Glands size of peas and walnuts in both groins.

* Read before the American Pediatric Society, Cincinnati, June 2, 1898.

Liver flatness above at sixth rib; edge felt three fingers' breadth below costal border. Edge of liver sharp and firm. Spleen felt running from left anterior superior spine across to umbilicus and thence upward under ribs in left nipple line. Notch a little above level of umbilicus. Edge smooth and hard. Slight enlargement of epiphyses.



SEVERE ANÆMIA WITH SPLENIC TUMOR.

Blood.	Hæmoglobin, - - - -	60 per cent.
	Red corpuscles, - -	4,340,000
	White corpuscles, - -	31,500

Owing to poor straining it was impossible to make a differential count of the white corpuscles at this time and the red cells were alone examined. They showed very marked variation in size. Poikilocytosis was extreme. Nucleated forms were very numerous. Of 100 nucleated cells, 89 were macroblasts and 11 normoblasts. Six of the macroblasts showed nuclear figures. Many of the nucleated, and some of the non-nucleated forms, were polychromatophilic.

A differential count of the white corpuscles was made from cover-slips prepared five days later, July 19, 1897. This resulted as follows:

Lymphocytes,	29.5 per cent.
Large mononuclear,	9.9 " "
Polynuclear neutrophiles,	56.5 " "
Eosinophiles,	.3 " "
Myelocytes,	3.8 " "

Strangely enough, nucleated red corpuscles were very much less numerous that at the preceding examination. While counting 1,000 white corpuscles, 17 nucleated red cells were seen, all macrocytes. Three of these showed nuclear figures. Polychromatophilia was much less marked.

The diet was regulated, and small doses of Fowler's solution ordered.

The child was not seen again until August 9th. The general condition was then somewhat better. The physical examination was unchanged, except that the spleen had diminished considerably in size. (See photograph). The blood was unfortunately not examined. The child was not seen again, but the mother wrote in answer to an inquiry, that it died on September 18th. There was hemorrhage from the bowels for two weeks before death, and the "bunch in the side could not be felt."

Before attempting to classify this case it may be well to consider briefly the peculiarities of the blood in infancy both in health and disease. The blood of infants under two years, normally differs in certain of its characteristics from that of adults. The hæmoglobin, although relatively high for a few weeks after birth, is, during the rest of childhood, relatively low. The number of red corpuscles is about the same or a little larger than in adults, averaging a little over 5,000,000 per cubic millimetre. During the first weeks of life there is more or less variation in the size and shape of the red cells, and nucleated forms are not very unusual. The number of white corpuscles per cubic millimetre is somewhat larger than in adults, averaging from 10,000 to 12,000. The relative proportions of the various forms of leucocytes are also considerably different. The limits, as given by Gundobin, are as follows:

Small mononuclear,	50 per cent. to 70 per cent.
Large mononuclear,	6 " " " 14 " "

Polynuclear neutrophiles, - 28 per cent. to 40 per cent
Eosinophiles, - - - - 1 " " " 10 " "

That is, the proportion of mononuclear forms is about three times as great as in adult life, while that of the polynuclear neutrophilesis only half as large. The mononuclear cells, moreover, are not merely lymphocytes, but vary much, not only in the size of the cell as a whole, but also in the size of the nucleus and in the amount of protoplasm. Finally, an increase in the number of eosinophilic cells, even if considerable, seems to be of less significance.

Blood changes develop more easily and more frequently as the result of various morbid conditions and diseases in children than in adults. All the changes seen in the blood of adults as the result of disease, are exaggerated in infancy. The tendency is always to revert to a younger or to the fœtal type of blood. All forms of blood disease in infancy are apt to be associated with splenic enlargement.

As the result of this tendency to exaggeration of changes and to reversion to a younger type, the red corpuscles show much greater variation in size and shape and many more nucleated forms than in similar pathological conditions in adults. Leucocytosis also develops more rapidly and to a greater degree. Its type, moreover, is not constant as in adults in whom the increase of white cells is almost entirely in the polynuclear neutrophiles. In children the leucocytosis is sometimes due to the increase of lymphocytes, sometimes to that of the large mononuclear forms, sometimes to that of the polynuclear neutrophiles and sometimes even to that of the eosinophiles. The general tendency, however, seems to be toward lymphocytosis, *i.e.*, toward the infantile type. This variation in the character of the leucocytosis is difficult to explain, except on the assumption that the proportions of the leucocytes correspond to certain tissue conditions and alterations which are at present unknown. The lymphocytes seem, however, to be especially increased in affections of the gastro-enteric tract. Leucocytosis is more apt to occur in blood conditions associated with splenic enlargement than in those without it. Myelocytes occur in less severe conditions and in greater numbers than in adults. The percentage of hæmoglobin is almost always relatively low.

Owing to the peculiarities just noted, the classification of the anæmias of children is at best a vexed one. They, as those of

adults, may be roughly divided into the primary and secondary, the primary being subdivided into chlorosis and pernicious anæmia. Chlorosis, with its typical symptom complex and blood, is not a disease of early childhood. Cases of progressive pernicious anæmia have been reported in young children, but they are all open to criticism, either because they do not correspond to the blood-type accepted for this disease, or because they are secondary. There is no evident reason, however, why this disease should not occur in infancy. In fact, the instability of the blood at this age would seem to predispose to its occurrence. The secondary anæmias may be divided, in accordance with the classification of Monti, into the mild and severe forms—anæmia levis and anæmia gravis. In the former the diminution in the specific gravity, hæmoglobin and number of red corpuscles is slight and the red corpuscles show no histological changes. In the latter the diminution in the specific gravity, hæmoglobin and number of red corpuscles is marked and the histological changes in the red cells are often considerable. In this form marked variation in the size, shape and staining qualities may be present and nucleated forms of all sizes and shapes are not infrequent. Either form may or may not be accompanied by leucocytosis. In all forms, whether or not accompanied by leucocytosis, the spleen may be enlarged. It is evident, moreover, from the above description, that no sharp distinction can be drawn between the various forms, but that all must merge into one another.

It is to the severe form of anæmia without leucocytosis associated with splenic tumor that the term "splenic anæmia" has been applied. There is no justification, however, for setting these cases apart as a special form of disease and giving them a special name, for there is nothing characteristic in the blood condition; the same condition of the blood occurs unassociated with splenic tumor and in connection with leucocytosis; splenic tumor occurs with other blood conditions and with a normal condition of the blood; both blood changes and splenic tumor occur together, as secondary manifestations, in the course of other diseases, notably, rickets. The splenic tumor must, therefore, be regarded either as an accidental association or as a result of the same cause as the anæmia.

Certain cases of severe anæmia associated with marked leucocytosis and with large splenic tumor have been described under the term "anæmia infantum pseudo-leukæmica." There seems to be

no unanimity of opinion among those who use this term, however, as to what constitutes the disease. Von Jaksch, who gave it its name, describes it as a form of anæmia of children whose symptoms and clinical course correspond to the picture of leukæmia. There is marked enlargement of the spleen, liver and glands, a very considerable leucocytosis, but no evidences of leukæmia on section. The course is less rapid and the prognosis better than in leukæmia. The increase in size of the liver and spleen is not proportionate as in leukæmia, that of the liver being relatively less than that of the spleen. The edge of the liver is sharp, not rounded, as in leukæmia. His examinations of the blood are unsatisfactory, and he gives no differential count of the white corpuscles. Luzet and Alt and Weiss describe the blood condition as follows: Constant diminution in the number of erythrocytes; constant more or less marked diminution in hæmoglobin; poikilocytosis; very many nucleated red cells, mostly of abnormal form and many showing karyokinetic figures; polychromatophilia of the nucleated red cells and many of the non-nucleated; pretty marked leucocytosis, always polymorphous. In addition there is always splenic tumor and more or less enlargement of the liver. They apparently attribute no diagnostic importance to the presence or absence of myelocytes. This description is the one which is at present the more generally accepted. Those who consider this blood condition characteristic are divided, however, as to the limitations of the disease. Some, who consider it always primary, would rule out those cases in which it develops secondary to rickets, syphilis or other anæmias, while others would include them. Careful comparison of the clinical histories and blood examinations of the cases reported as examples of this disease show still further discrepancies in the conception of the disease.

There is nothing characteristic in the changes described in the red corpuscles. They may be seen in any severe anæmia. In the same way there is nothing characteristic in the leucocytosis; it is merely a question of degree. Fischl has found the same type of blood in cases of rickets both with and without splenic enlargement. Moreover, cases of progressive anæmia with enlarged liver and spleen do not always show this condition of the blood. In addition, ordinary secondary anæmias have been seen to develop this blood-type while under observation. Von Jaksch claims to have seen it change to a leukæmia, and Muller to a per-

nicious anæmia. These last observations must be considered as doubtful, however. It is evident, therefore, that there is nothing in the etiology, clinical history or blood of the so-called "anæmia infantum pseudo-leukæmica" to justify its acceptation as an independent disease. It is rather to be regarded merely as a severe type of secondary anæmia which may arise as the result of many diseased conditions. Its special peculiarities, marked leucocytosis and large excess of nucleated red corpuscles, are in no way characteristic, but merely due to the age of the patients. While these cases are not sufficiently characteristic to be considered as examples of a separate disease, they are of importance in that they emphasize not only the heterogeneous character of the anæmias of infancy, but also the difficulties in the way of their classification.

In the light of our present knowledge, therefore, a very simple classification is alone justifiable. The following modification of Monti's is, I think, a fairly satisfactory one:

SECONDARY.—Mild anæmia.
Mild anæmia with leucocytosis.
Severe anæmia.
Severe anæmia with leucocytosis.

PRIMARY.—Pernicious.
Leukæmia.

In all of these forms there may be greater or less splenic enlargement. Splenic tumor, therefore, is of little or no aid in the differential diagnosis of the anæmias of infancy. Under the head of severe anæmia with leucocytosis must for the present be included all those anomalous cases which do not correspond to the type of either pernicious anæmia or leukæmia. That is, this class includes the cases which have hitherto been described as "anæmia infantum pseudo-leukæmica." Unfortunately there is practically no data as to the type of blood of either pernicious anæmia or leukæmia in infancy. For the present, therefore, they must be considered to be the same as in adults.

My case illustrates very well the difficulties in the way of classification. The histological changes in the red corpuscles and the great preponderance of large nucleated forms suggest pernicious anæmia. The diminution in the number of red cells is slight, however, and much less than that which usually occurs in this condition. Splenic enlargement to the degree present in

this instance is at least unusual. The number of white corpuscles and their relative proportions is not, however, inconsistent. The enlargement of the liver, spleen and glands suggests leukæmia. The increase in the number of leucocytes is only moderate, however, being much less than that which usually occurs in leukæmia. The percentage of myelocytes, moreover, is small, being no larger than that which is often met with in severe secondary anæmia of any sort. The clinical history and blood correspond pretty closely to those of "anæmia infantum pseudoleukæmica," as described by Luzet and Alt and Weiss. This condition, however, as already stated, cannot be considered as a disease *sui generis*, but merely as a severe form of secondary anæmia with leucocytosis. My case, too, must therefore be regarded, I think, simply as an example of this large and irregular class of severe secondary anæmia with leucocytosis. The cause of the anæmia in this instance is undoubtedly to be sought in the general malnutrition resulting from improper food. The splenic tumor must be regarded as merely a coincidence, a result of the same cause. That it is not an essential feature of the case is shown by the fact that it became smaller as the case progressed, probably finally disappearing entirely.

317 MARLBOROUGH STREET.

LITERATURE.

ALT u. WEISS: Centralblatt f. d. med. Wissenschaften, 1892, XXX., 433.

ANDEOUD: Rev. de. méd. de la Suisse rom., 1894, 507.

BAGINSKY: Archiv. f. Kinderheilk., 1891, XIII.

BANTI: Dell' Anæmia Splenica. Florence, 1882.

CABOT: Clinical Examination of the Blood.

EPSTEIN: Prag. med. Wochenschr., 1894, 6.

FELSENTHAL: Archiv. f. Kinderheilk., XV., 78.

FELSENTHAL u. BERNHARD: Archiv. f. Kinderheilk., XVII., 333.

FISCHL: Zeitschrift f. Heilkunde, 1892, XIII., 277.
Wiener klin. Wochenschr., 1894, VII., 241.

GLOCKNER: Zur Casuistik der Anæmia Splenica. München, 1895.

GUNDOBIN: Jahrb. f. Kinderheilk., 1893, N. F., XXXV., 187.

HAYEM: Gaz. des Hôpitaux., 1889, No. 30.

HOCK u. SCHLESINGER: Centralblatt f. klin Med., 1891, XII., 873.
Hæmatologische Studien, Leipzig u. Wien, 1892.

LUZET: Études sur les Anémies de la Première Enfance et sur. l'Anémie Pseudo-leucémique. Thèse, Paris, 1890.
Archives Générales de Médicine, 1891, 597.
La France Médicale, 1891, XXXVIII., 771.

MONTI: Wiener med. Wochenschr., 1894, XLIV., 401.
Wiener med. Presse, 1894, XXX., 1552.
Archiv. f. Kinderheilk., 1884-5, XVIII., 161.

MONTI u. BERGGRÜN: Die chronische Anämie im Kindesaltes.

MORSE: Boston Med. and Surg. Journal, 1897, CXXXVI., 369.

MULLER: Charité-Annalen, 1889, XXIV.

REHN: Gerhardt's Handbuch d. Kinderkrankh., 1878, III.

ROTCH: Pediatrics.

SCHIFF: Zeitschrift f. Heilk., 1890, XI.

SENATOR: Berlin. klin. Wochenschr., 1892.

SOMMA: Allg. Wiener med. Zeitung, 1891.

STENGEL: Twentieth Century Practice of Medicine, VII., 460.

TAYLOR: Guy's Hospital Reports, 1896, LII., 173.

VON JAKSCH: Wiener klin. Wochenschr., 1889, II., 435.

VON LIMBECK: Klinische Pathologie des Blutes, 1896.

WEISS: Jarhb. f. Kinderheilk., 1893, XXXV., 146.

WEST: Med.-Chir. Tr., 1896, LXXIX., 323.

DISCUSSION.

DR. JACOBI.—I am delighted to find that a gentleman who has been studying the blood for years and who is intimately acquainted with it in all its phases, should feel obliged to protest against the multiplication of names and diagnoses. The result of his studies has led to the conclusion that the names we now possess are ample for making our diagnosis, always taking into consideration that the gradual transition and mutability of several forms of anæmias are well established and may occur. We do know, for instance, that cases at one time recognized as pseudo-leukæmia, may afterward turn into leucocythæmia, etc. If I understood correctly, there was in this case enlargement of the

spleen and liver in the beginning. It is not necessary that those be a part of the disease; they may have existed before. The spleen got a little smaller after a while and it appears that is not the case in leucocythæmia. There were 4,100,000 red blood cells and 30,000 white, that is a proportion of 1 to nearly 140, which comes near the boundary line of leukæmia. Afterwards no other examination of the blood was made. The doctor states that there was a poikilocytosis, so it seems to me the case should be claimed to be one of so-called pernicious anæmia. The lymph bodies were swollen all over. That with the diminution in the blood cells would give us the appearance of pseudo-leukæmia, Hodgkins' disease. I understand that a *post-mortem* was not made. If it were not for the poikilocytosis in the case I would say that it was a case of Hodgkins' disease, but the poikilocytosis characterizes it as a pernicious anæmia. There is no reason why these two conditions should not occur at the same time, under the same or similar or different unknown circumstances.

DR. FREEMAN.—I had a case a year ago in which the appearance of the child was much like this. There was considerable emaciation, enlargement of the liver and spleen, considerable anæmia with leucocytosis. The diagnosis was not made until autopsy, when we found an abscess of the left kidney, which had not caused a large tumor. It had produced a waxy liver and a waxy spleen. We also found tuberculosis present.

DR. MORSE.—It seems to me that in the light of the knowledge which we now possess of the different forms of white corpuscles, as shown by differential staining, it is too late to speak of the relative proportions of white and red corpuscles in making the diagnosis between leucocytosis and leukæmia. The number of red corpuscles depends on one factor and the number of white corpuscles on another. There is no necessary relation between them. They must, therefore, always be considered independently. Moreover, there is no absolute number of white corpuscles which can be regarded as fixing the line between leucocytosis and leukæmia. In leucocytosis the increase is largely in the number of polynuclear neutorphiles, although in infants it may be in the lymphocytes. In splenic-myelogenous leukæmia, on the other hand, while all forms are increased, the bulk of the increase is due to the presence of abnormal white corpuscles, the myelocytes. The presence of a small percentage of myelocytes, even as high as 5 per cent., does not justify the diagnosis of splenic-myelogenous leukæmia, however, as a small percentage of myelocytes is found in many severe blood conditions, especially in children. The percentage of hæmoglobin in this case is much lower relatively than that of the red corpuscles, a condition which is the opposite of that usually excepted for pernicious anæmia. The number of leucocytes is increased, which is not

the rule in pernicious anæmia. This might, however, be due to some other cause and would not rule out pernicious anæmia. The histological changes in the red corpuscles alone correspond to the blood type of pernicious anæmia, but, as already pointed out, the tendency of the blood in disease in infancy is to revert the fœtal type, and the presence of poikilocytosis and of nucleated cells in infancy is of much less diagnostic value than in adults. As already stated, the case can only be regarded, therefore, as one of severe secondary anæmia with leucocytosis.